A Study Guide In Organic Retrosynthesis: Problem Solving Approach

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Lecture - 02
Introductory Remarks (Contd.)

So, welcome back. So, with the last lecture we have discussed that why we want to do organic synthesis and as I said it is one of the core discipline of chemistry and you want to make organic molecules in a sufficient quantities in a cost effective or economical viable manner so that this molecule can directly benefit to human society.

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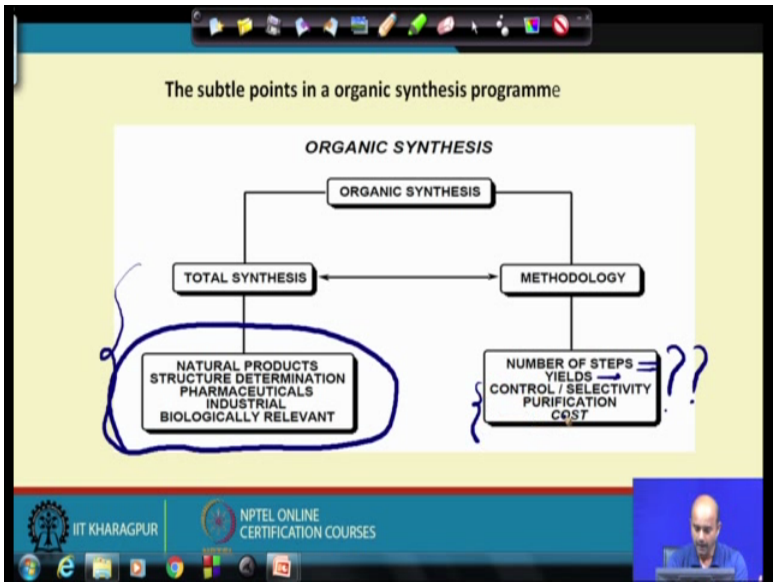

Now, this set we will try to focus our ways that what are the viable ways to make organic molecules in a cost effective or efficient way. The organic synthesis as I said this slide you can see we have been classified into 2 points or 2 subsections. So, this is the central area it have been classified in 2 areas where total synthesis comes and methodology comes.

Now, this total synthesis and methodology are closely interlinked you will be using water methodologies, these are basically single step transformations like a fatigue reaction, like a so on oxidation, like a physic oxidation. So, this is our single step methodology and you will be using those methodologies to make a target molecule.

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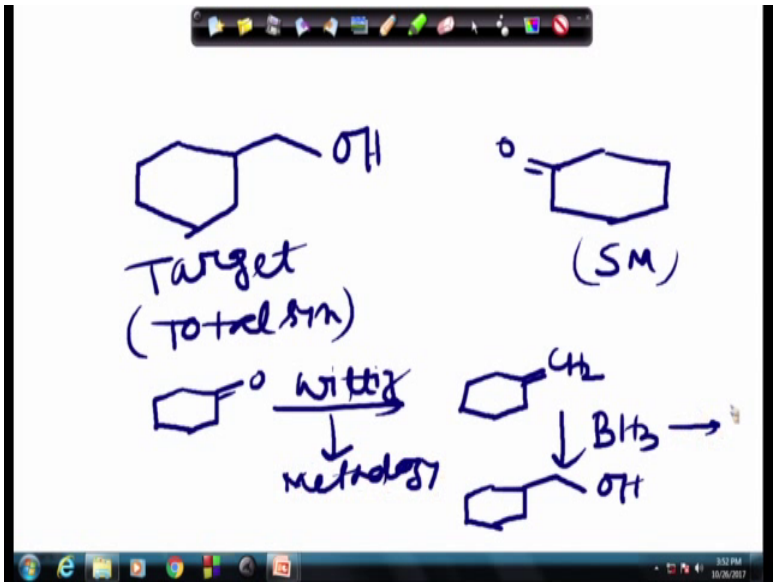

Let us see a simple viable things I said you have to make a molecule and this is the target molecule target and this is your starting material. So, this is your target means this is your total synthesis target synthesis target and this is your starting material.

Now, if you can correlate basically what are the reactions you need you will be using a wittig reaction first to convert this compound to this cyclohexene and this you are doing a hydroboration reaction to get this target molecule. Now this wittig reaction is a transformation is basically a methodology a single step transformation, but very useful methodology hydroboration is a methodology. So, these things are methodology and by using this methodology you are getting a target molecule. So, this is your interlinking between the methodologies and that total synthesis that is why this these 2 terms are basically interlinked.

Finally as I said earlier total synthesis of target molecules then target molecules can be anything as I said this this could be natural product you can take the help of structural determinations, there could be lifesaving drugs or pharmaceuticals they are industrially important compounds like pesticides herbicides and they are biological relevant definitely all the target molecules; should have biological significance simply for making a academic pursuit that if the compound does not have the biological importance probably our effort is not that much counted.

Now, when we talk about methodology in this case our prime concerned will be this 2 these factors number of steps how many number of steps is required yields; yields for individual steps, if the methodology is very high yielding then your effort is counted and the point is controlled if the methodology is can control the reactivity or selectivity let us say as I said this terminology control the final point.

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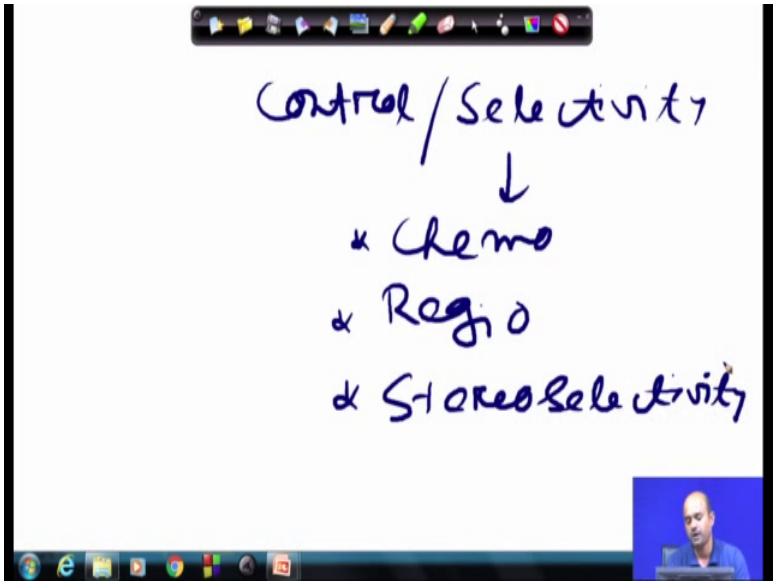

Control or selectivity when we talk about selectivity it basically implies everything it implies chemo selectivity, it implies Regio selectivity, it implies stereo selectivity

So, all these terminologies all these points need to be clearly addressed in your synthetic design or synthetic pathway. Then your entire pathway will be quiet viable and as the as the overall pathway is efficient effective your cost will be definitely come down. Now cost is one of the factors where industrial people or pharma sector pharma industry people will be much more interested, but anyway we will be trying to figure it out all those certain points in our effective synthetic pathway design. So, our as a set our main focus is a guide to retrosynthetic analysis.

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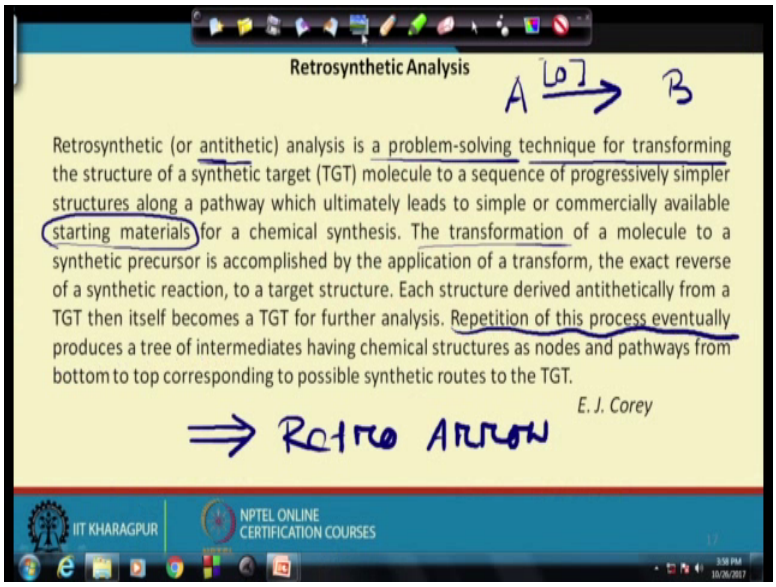

Now, what are retrosynthesis as I said earlier retrosynthesis is basically the way of thinking back.

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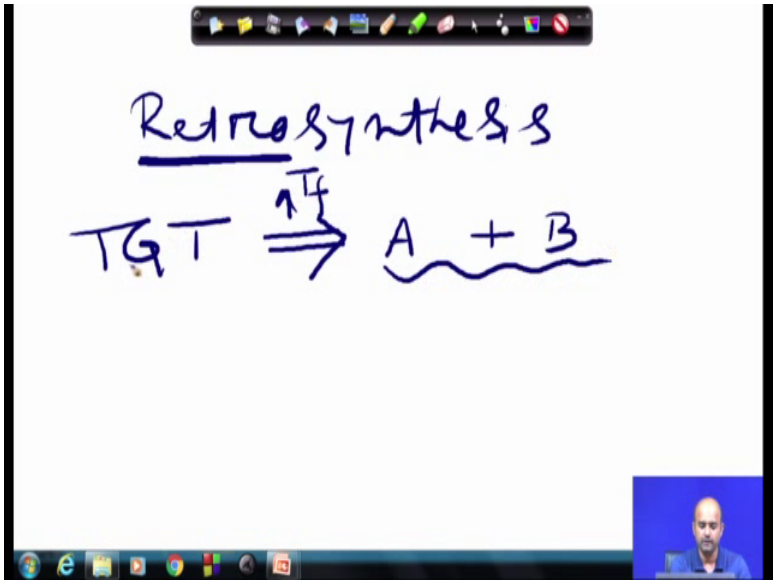

Retrosynthesis is the term retro; retro is nothing it basically give you a backward approach. So, you have a target molecule the target could be anything you device a pathway which will basically give you 2 different intermediate, which are basically chemical components and you device that suitable transformations or T f is called transformations which will be explained in the terms of grocery and other things at this intermediates A and B undergoing a suitable transformation will give you target. Now this the backward approach is called as retrosynthesis it is basically a programmed

approach it is a logical driven approach just by seeing the structure you can think about what are the suitable into synthetic pathways. So, we will be coming to those things little bit later on.

Now, let us go back to Professor E. J. Corey's standard definition what Professor E. J. Corey says about retrosynthetic analysis. Retrosynthesis as I said retrosynthetic analysis sometimes it referred as antithetic analysis is a problem solving technique is a problem solving technique for transforming the structure of a synthetic target a given molecule to a sequence of progressively simpler structures. So, as I said a complex structure has been fragmented into a simplified structures and then it lead to a commercially available starting materials because you have to start from a building block starting the materials. So, a complex molecules can be simplified to a commercially starting materials. So, that you can start using those starting materials for a given pathways the transformation of a molecule to a synthetic precursors is accomplished by the application of a transform as I said transform is basically a sequence of reaction.

Now, as we used a reverse arrow this arrow is often termed as retrosynthetic arrow a retrosynthetic arrow retro arrows you can call it is just opposite to the forward arrow, when you do a forwards reaction you put a starting material A you do put A arrow you put some reagent let us say you do you are doing A oxidation reaction, you get B this is a forward arrow. If you do this arrow it is called retro arrow which was done in a piece of paper or piece or you can even do with a computer. So, this repetition of this whole process eventually lead to a tree of intermediates I will explain it again.

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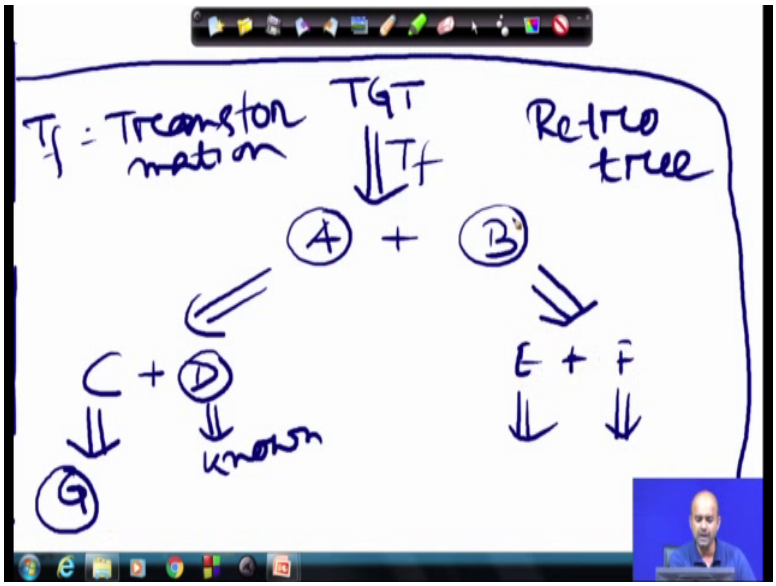

So, we have a target molecule and you do a retrosynthesis arrow it is called backward arrow you come to intermediate A plus B. Now this a might be a complex molecule it is not commercially available. So, device a retrosynthesis for a first and that basically will give you few another intermediate C plus D. This B it is also may not be a commercially available, then you come back here E plus F. Now you find that might be D is commercially available you said this material is known material. Now C C may not become commercially available you again come back and devise another retro pathway for here also same thing might be applicable depending on the source of the materials.

Now, this entire pathway this entire pathway this entire pathway or you can call it as a branching pathway you are starting from a target molecule this branching pathway is called a retrosynthesis tree. It is a retro tree; tree having many branches and this is a retro branching. Now what is this backward arrow means where basically you are doing some transformation T f; T f is abbreviated as transformation any single transformation. So, let us say for oxidation reaction reduction reaction it is named as transformation reaction and then you come back to these things finally, you come that D is a commercial starting material even G can be A commercially available.

So, now you start forward you start with G and D mix them together by A chemical reaction you get A similarly you mix E plus f you get B then you couple A plus B with A

suitable transformation you come to a target molecule this is exactly what we do in the retrosynthetic analysis.

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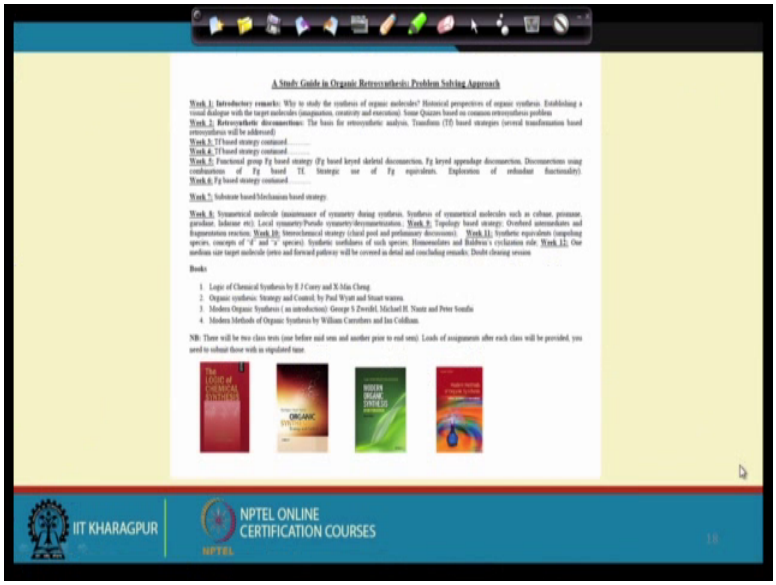

So, what we are trying to do basically our entire lecture is divided into 12 weeks and if you see this course curriculum we will be basically trying to cover different aspects. This week one this particularly week we will be talking about introductory remarks at the sand some of the groceries how to choose a target how to think about a target at the end we will be talking about some, quizzes is a rapid fire round or you can see that some of the structures how they can be efficient limit and then if you see the syllabus from week 2 onwards we will talk about deep detail of organic retrosynthetic analysis.

The textbook couple of textbook might be useful for you this one logic of chemical synthesis has been written by professor E J Corey. If you can buy this book is fine otherwise you have to rely on this lecture material there are books named organic synthesis strategy and control, number 2 books by Paul ward and Stuart warren is a very good book, number 3 modern organic synthesis is written by George Zeufel and his coworkers this is a very good book, number 4 this number 4 book is (Refer Time: 12:01) book which is also very important. And eventually throughout our entire discussion we will try to have a problem solving approach we will take from target molecules, which you do a disconnection and then you try to find it out that how this basic understanding will help you to design a pathway, the problems have been taken from different exams.

So, basically I will try to give a emphasis that whether after starting this course you will perform well in those particular exams and that is our main idea.

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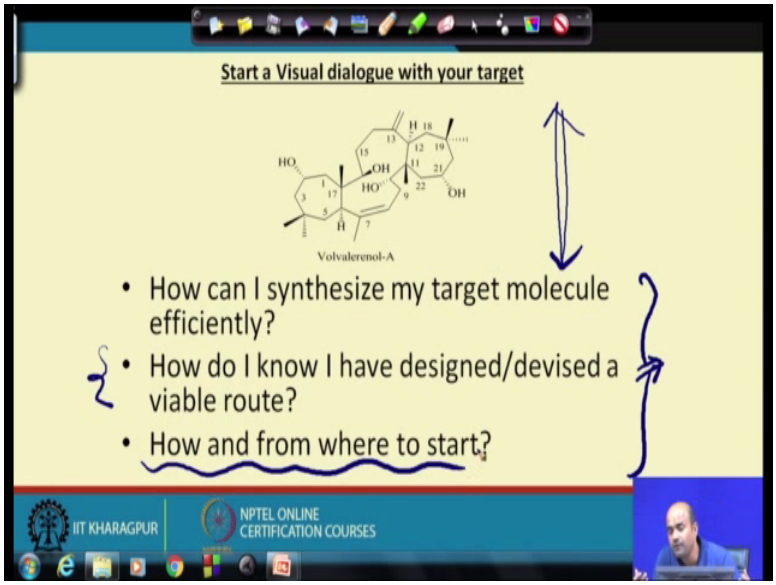

Now, initially once a target molecule is given to you a target molecule is given to you I have given a target molecule it is a huge big molecules the initial point once you see the target molecule, I said just have a look just have a focused look focused look and you are initially you need to ask a 3 questions to yourself that how can I synthesize my target molecule efficiently. Now the initial question you need to ask how do I know I have designed a devised a viable route. Now you might be a beginner in this field. So, once you design a pathway you consult to your teacher you consult a expert who is known to this field for many days and then you show his pathway show your pathway that is why I have devised a pathway will you check it and then you have to execute it.

Organic synthesis is basically a practical field once you design a pathway you have to practice in the lab. So, you have to put the reactions you have to get the product you have to identify you have to characterize it and then finally, once you come to the target you have to check it is analytic data's which should be matching with the original one then your final goal is achieved.

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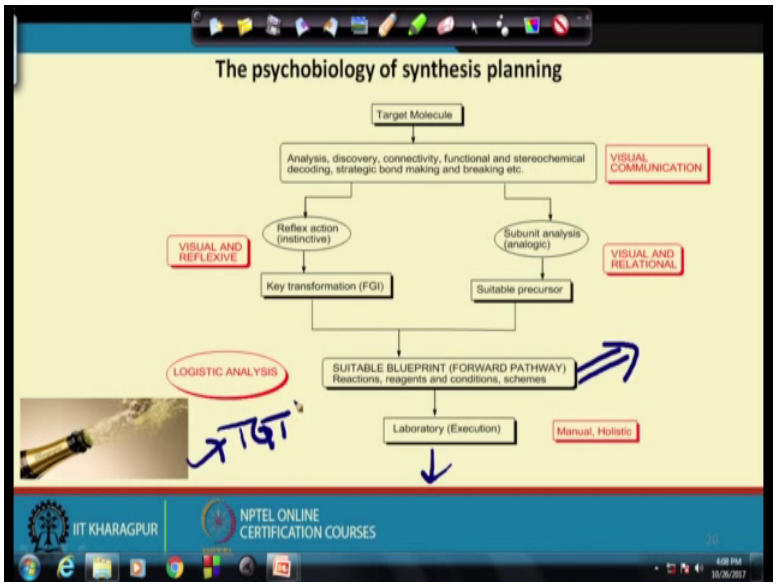

So, eventually throughout this Pathway, now a tentative designing strategically pathway I have tried to provide here that once the target molecule is given to you what should be your ideal approach. I set the target molecule at the extreme top. So, first you see the target molecule by your open eyes and I always try to focus it out that you start communicating with the molecule it is not by one to one talk, you say visual dialogue just by seeing the molecule if it is possible you start a visual dialogue this is the functional group which I can make a make a disconnection by a witting reaction by a so and reaction.

So, that is the I called visual dialogues you see the molecule closely analyze first closely analyze first then you see the connectivity functional group stereochemical contents all these points will be coming, then you choose what strategic bond making is needed that is why we called visual communication is very important point you see a molecule start a visual communication. And visual communication basically is a reflexive action it is like a reflex action you see the molecule straight way you said this is the molecule I want to make and let us say I have given you a molecule a target molecule now what your visual instinct says.

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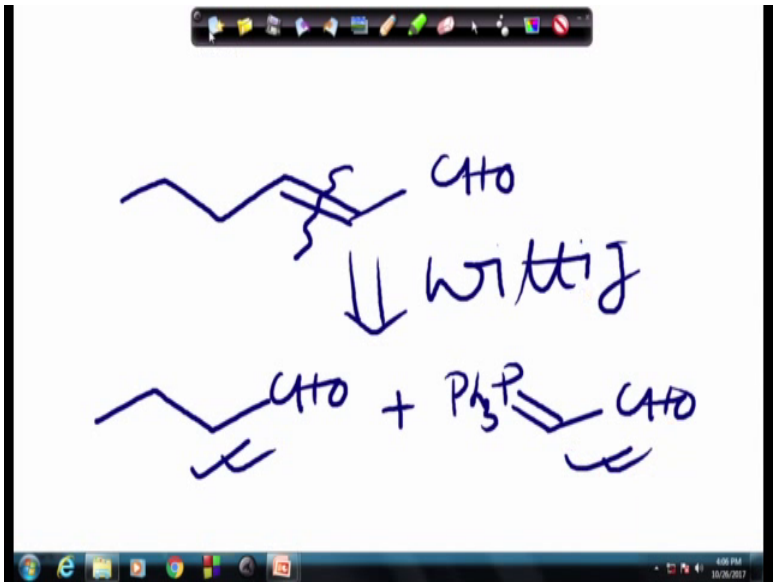

I can do this molecule by a wittig reaction that is fine you can do it. So, what are the intermediates you need to do you just need to do a break this is called a retrosynthetic disconnection or breaking the bonds. So, you put a aldehyde here and do a wittig reaction with a suitably substituted wittig elite. So, this is your starting material this is your starting material which may be commercially available and you are (Refer Time: 16:12) with in transformation. Now these things it is your visual communication now let us say you see the molecule first and then you start a visual communicating.

It is a reflexive action and then you need to figure it out what are the key transformations what are the key transformations the term is called FGI, FGI we will be abbreviating it later on is called functional group interconversion functional group interconversion. Sometimes you need to analyze the through a logical way once your visual part is done then you go back to deep into the logic, now what are the chemical logic that is why it is called visual as well as relational means try to find the relation that which bonds can be made by which transformation and then you try to correlate what are the suitable precursors is available to you what are the commercial starting materials available to you.

So, once you have choked out the whole thing then you do a logistic analysis of the entire pathway you do a logistic analysis of the entire pathway and then you design a suitable blueprint in a piece of paper or a computer and then you try to analyze the whole

pathway in the forward pathway which is called forward pathway because you have to make sure your design pathway works in the lab because organic chemistry nothing it is a practical chemistry.

So you will have to execute it in the lab and once you achieve the target molecule probably you can enjoy it with a bottle of champagne with a bottle of wine because this is the most rewarding experience in your probably if you choose synthetic organic chemistry as your career, but this could be a one of the rewarding experience once you achieve the target molecule the target has been achieved by your design pathway and you can enjoy it. So, these things we will be trying to figure it out in our next things.

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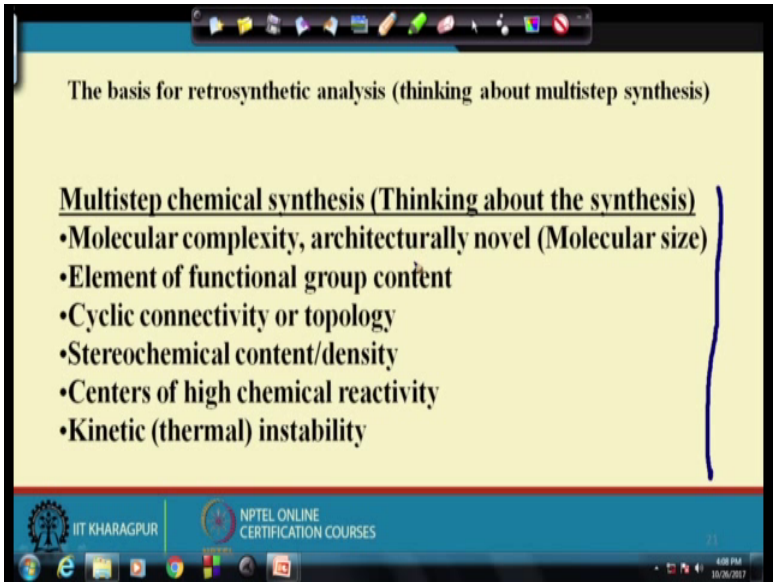

So, once you see a target molecule as I say you have to basically look into 6 different points you have to basically look into 6 different points what are those points I have been have been classified those points here 1 2 3 4 5 6.

At the very beginning we will always look for a as I said molecular complexity now go back to it is slide where you can find it that what exactly is it. So, the first point what is the target is given to you is CVS molecular complexity that how complex a molecule can be.

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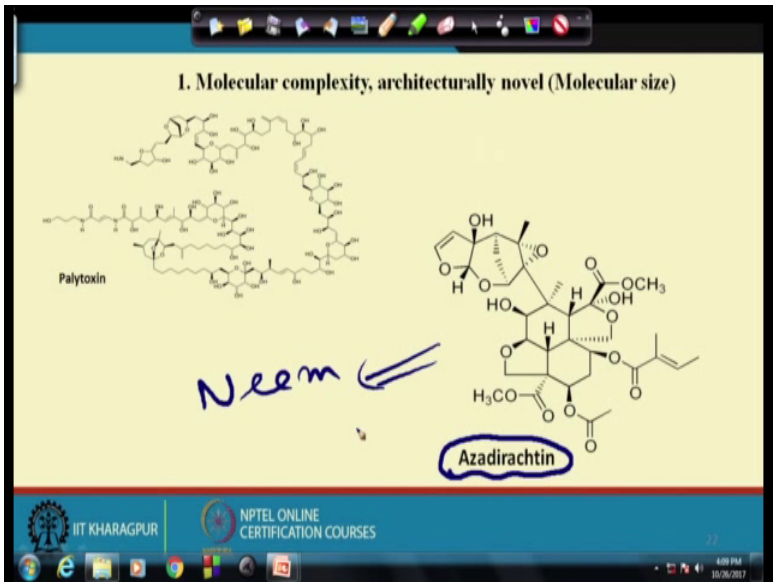

But definitely do not worry throughout our discussion we will talk about the molecule which is not that complex this molecules are really complex, we will talk about a bit simple molecule very simple molecule which you can essentially do it by your acquiring knowledge this particular molecule is very important Azadirachtin. This molecule is basically nothing it have been isolated from our own Indian Neem tree now you all of us know that Neem tree has having a potentially medicinally significance.

It can cause; it can give you a enormous product it can help you in many ways now this compound Azadirachtin it is a complex structure, but essentially these kind of molecules can be made.

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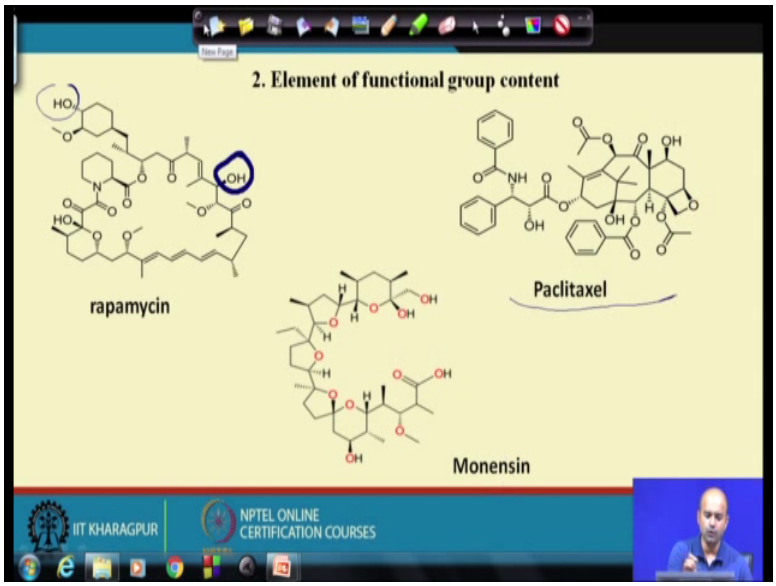

So, fine then you check the second point element of functional groups content then what are the functional groups present in your target molecule, now see the molecule rapamycin you see there are there are there are couple of hydroxy group on a secondary hydroxy group here. So, there are couple of secondary hydroxy group here in the rapamycin you have a secondary hydroxy group you have a secondary hydroxy group, you have a quadrant hydroxy group here, you have amide, you have ketone, you have ester.

So, these are the functional group you have olefin certain olefins you have a trice olefins triple unsaturation all are E E olefins E olefins E olefins Paclitaxel or taxel the very potent antitumor compound. If you see a structural complexity and functional group content you see this molecule is richly functionalized same like Monensin. So, eventually you have to go for this functional group content of a given molecule.

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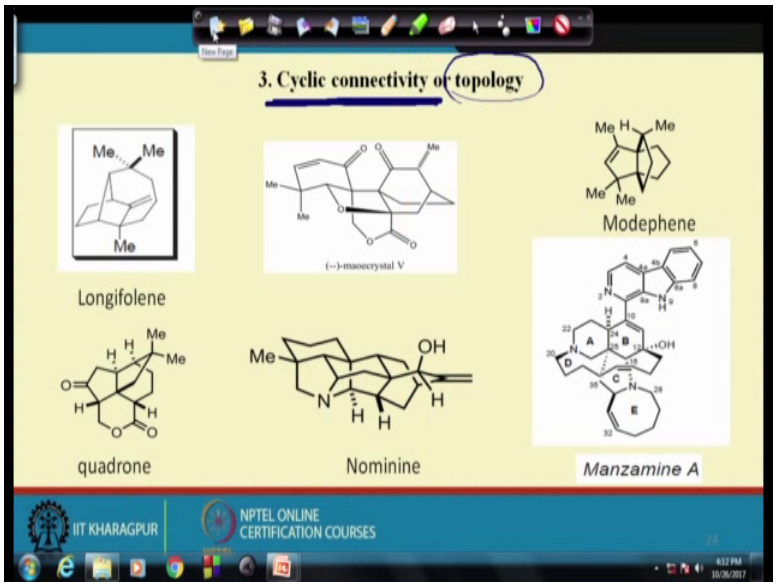

Next point when you see a target often the target molecules are very complex and then basically we will try to focus it out particularly one point which is cyclic connectivity. The how different rings are present in a given molecule now this particular terminology topology; topology we have not used in synthetic organic chemistry topology was a terminology often used in the mathematics and geometry, but in synthetic organic chemistry topology means how the molecule is cyclically or how it is cyclic connectivity let us emphasize a little bit more on topology.

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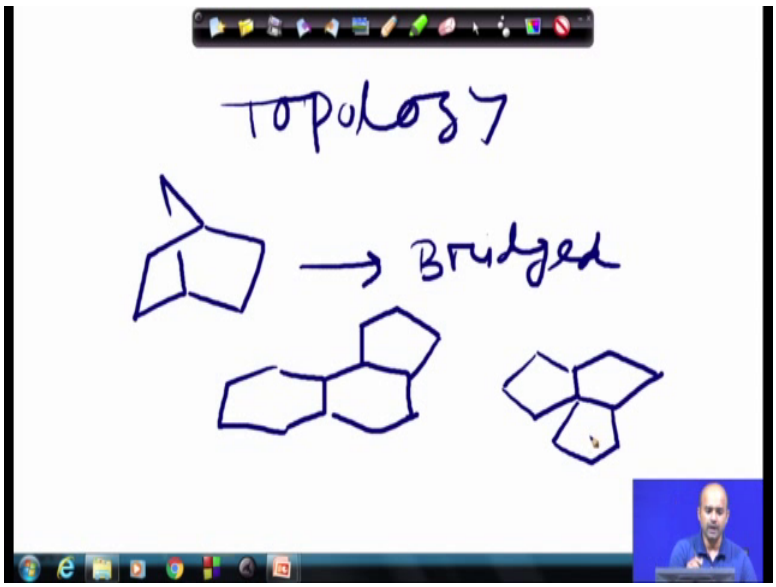

Topology basically says that how this molecule or cyclic groups are connected now this is a very unique topology this topology is basically give you a bridge structure a bridge like structure a bridge structure a bridged unit this is a unit topology 2 cyclohexane being linearly fused, you can have some extra topology 2 cyclohexane with a with a linearly fused angular fused cyclopentane there are topologies which is very useful 2 cyclopentanes linearly fused. Then you can have a angularly fused cyclopentane these are called triquinines then those are basically naturally occurring products you can have a pretty interesting topologies.

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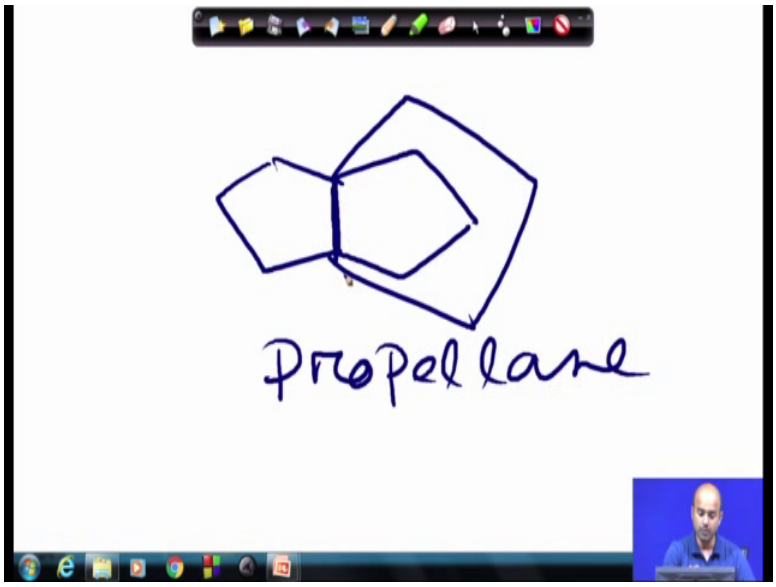

Let us say we will talking about topology which is very interesting you can have a topology which is something like this 5 member 5 member 5 member, but they have same axis this is called propellane based compound propellane basically is a propeller based on propellane; they have a common axis this axis it is common. It is again a triquinine, 3 cyclopentane rings fused in a through a common axis common bond and this is the terminologies which will be often used. Now we see that cyclic connectivity particularly for this molecule longifolene see longifolene it is having a bridged structure here bridge structure here and then we are having a from the bridge structure you have a cycloheptane ring.

It is very unique cyclic connectivity there are many interesting molecules this one as I said in my just now we have talked about is named as Modephene. Now modephene is a

propellane based compound it is having a common axis here and 3 cyclopentene rings attached here. So, this are the points you are basically want to have a look.

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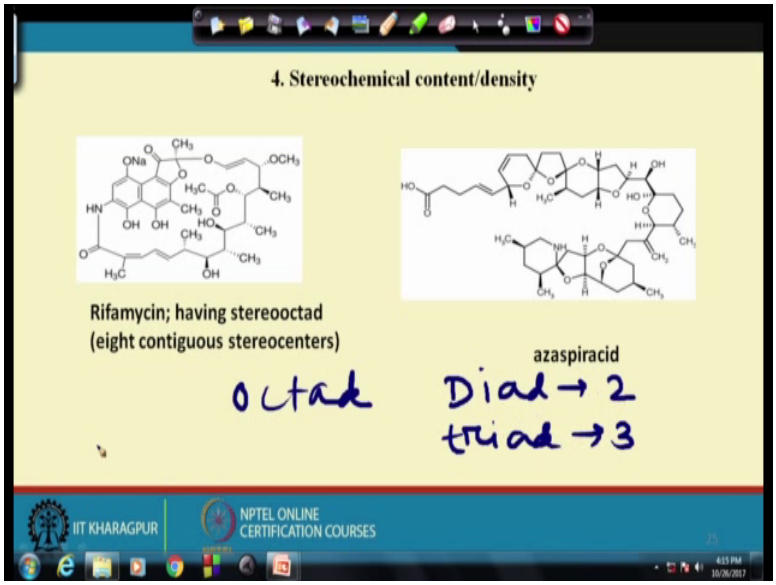

Next point is 4 we call it stereochemical content or stereochemical density, basically all the complex natural products we often deal with stereoccnters means you have to make a single stereoisomers out of N number of possible compounds. Now definitely the more complex the molecule the number of (Refer Time: 23:57) will be more and that causes significants challenge significant challenge, you see this molecule Rifamycin you will see this particular point rifamycin is having stereooctad. Now what are stereooctad octad means 8 stereocenters together you see 1 2 3 4 5 6 7 8; it is a octad if you have 2 stereocenters it is called Diad if you have 3 stereocenter; it is called triad 3 means 3 stereocenters.

Now, sometimes we use some terminologies which is called that contiguous.

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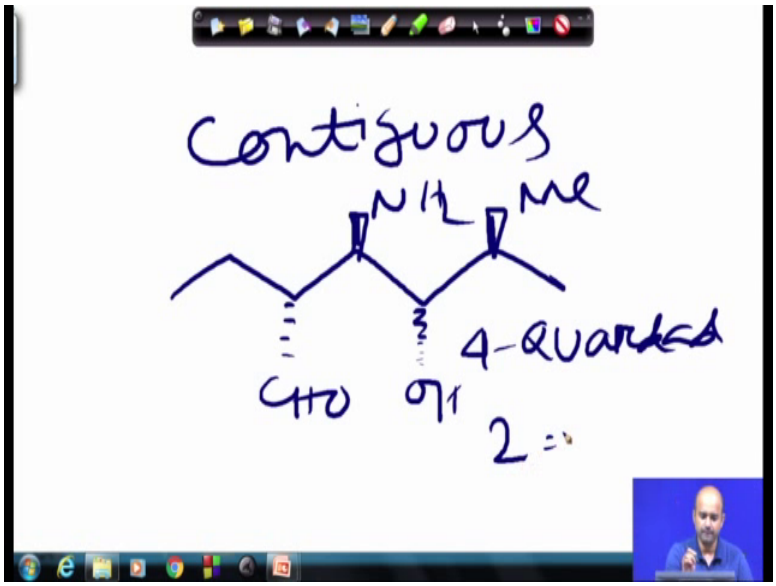

Contiguous means continuous stereocentre let us say you are having a chain of something like this and you put your stereocentres something like CHO NH 2 putting a OH putting a methyl. So, these are basically continuous stereocentres which are termed as contiguous and here how many stereocentres 1 2 3 4. So, you can basically call this molecule as a stedio quadrant or Quadrad. So, 4 stereocentres are there if it is 2 you can call dietary diad 3 triad 4 quadrad 5 pentad something like that 6 hexad 7 heptad 8 octad.

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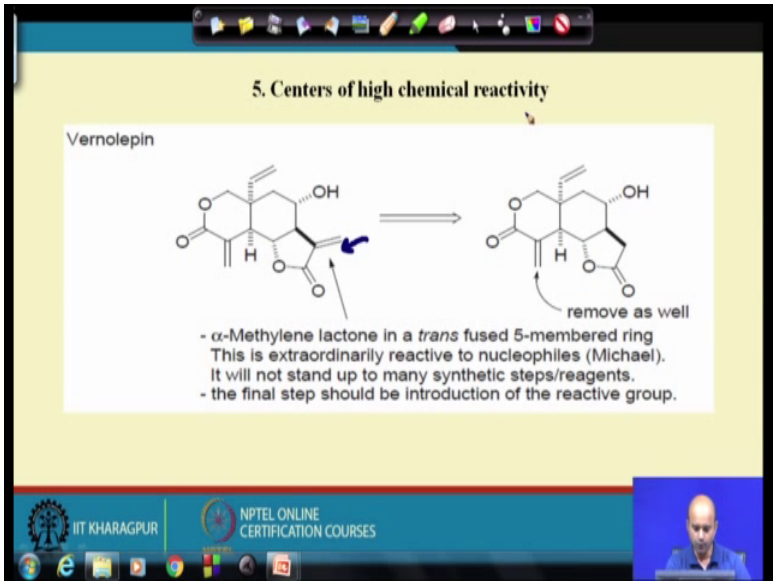

So, stereochemicals continues the next point which is just now we talked about so this is the eventually next point we will be saying centers of high chemical reactivity this is very important sometimes the target molecule might contained a group which is pretty much chemically reactive. Let us say for this case this groups is highly electrophilic in nature it can accept couple of Michael acceptors here it is highly reactive and make sure if your target molecule does have a highly chemical reactive group, you need to introduce those groups in a later part of synthesis because if you continue the synthesis by using this groups in between if you can use some neutrophilic condition this group this groups would not be stable it can undergo a reaction.

So, make sure this kind of high chemical reactivity group should be introduced at the late stage of the synthesis which is basically written here. So, you can take it as a guideline.

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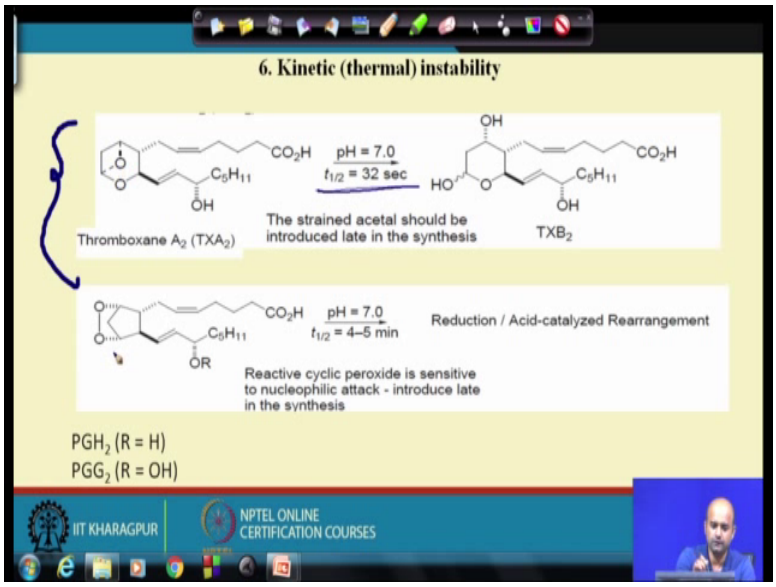

Some the sixth point was it kinetic instability many of the target molecules sometimes are not very much kinetically stable in the reaction conditions. Say for example, you have if you have a natural product which is called thromboxane thromboxane having a oxytane group 4 member oxygen containing group. As well as it is having a extra oxygen which is nothing basically a acetyl or ketyl now you put little bit neutral condition P H 7 this compound instantly as it get decomposed or opens up the acetyl ring t hub is only 32 seconds. So, means that the strained acetyl group should be introduced in the late stage in the synthesis you cannot continue this part as a starting material then you can make this

bond because this is very unstable same thing can applicable for this part also this potion of the (Refer Time: 27:32).

So, those are the finer points which you always need to take care.

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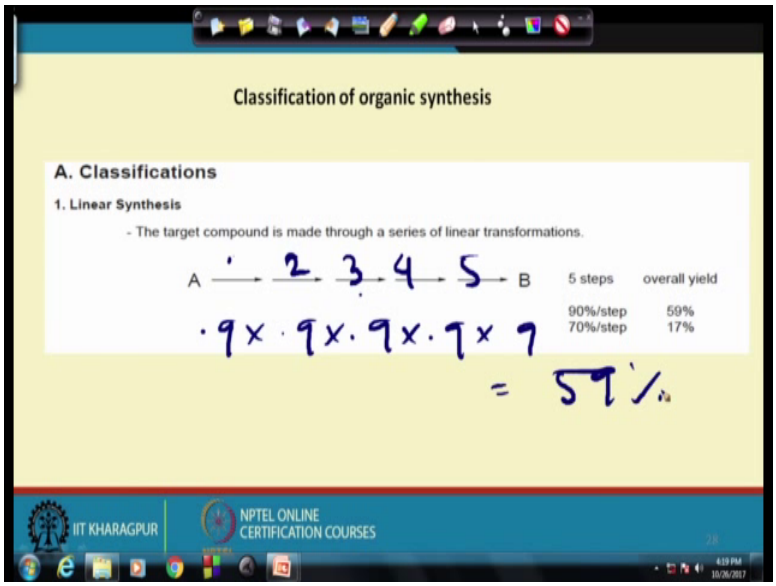

As I said we will try to give you little bit classification the organic synthesis is based on several ways the first one is linear synthesis, linear synthesis probably we will stop it here for today's discussion linear synthesis means that you start with an agent or study material A you keep on doing linear steps. So, 5 steps we said here 1 2 3 1 2 3 4 5 that gives you a target molecule. Now in each step is 90 percent yield. So, you are having 0.9 into 0.9 into 0.9 into 0.9 into 0.9 into 0.9.

That basically counts 99 percent of overall it. So, linear synthetic steps are often regarded as a little bit disadvantageous, because you are not having any branching and this effective yields at the end will be reduced, on the contrary if you are having a different path as I have said let us say for a convergent pathway, where 2 linear paths can be merged in a certain points.

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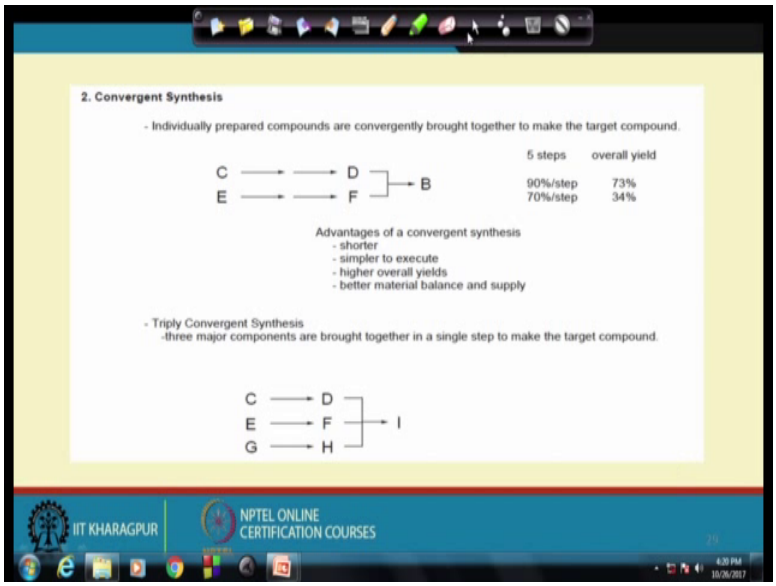

Let us say start with C you go 2 linear path to D you come to E is a another starting material come to F now these 2 branching these 2 linear path now merge.

So, your affective over a yield is now increased because 0.9 into 0.9 0.81 then 0.9 is 0.7 2. So, yield is now 73 percent because you are now having quite a different ball game. So, always is advisable that you follow a branching pathway or convergent pathway. So, branching pathway is always advised sometimes we have triple convergent means there are many branching pathways if your molecules are complex you can have branching pathways. So, linear pathway you always try to avoid, but for simple molecule linear pathway is always linear pathway is always and probably in our discussion we will more of talking about linear molecules.

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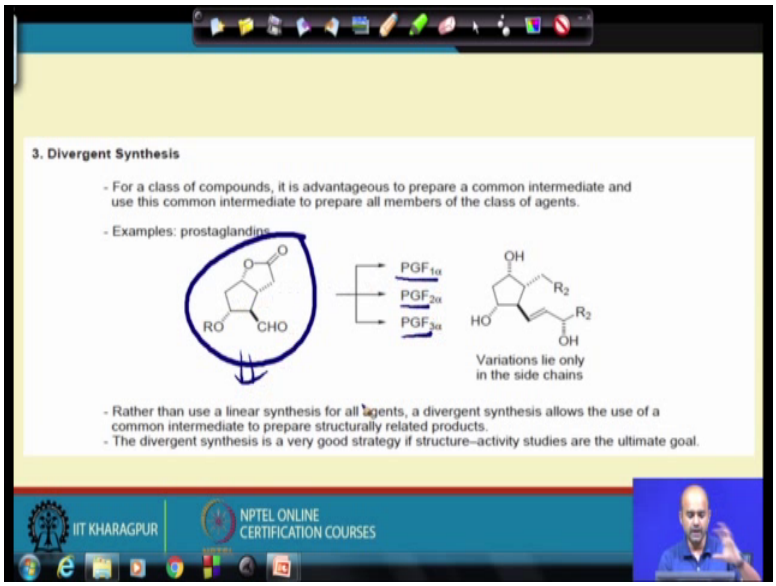

Divergent is another terminology it means that if you are having a intermediate something like this where from you can synthesize different target molecules say for this instance is this molecule can lead you this target this target this target.

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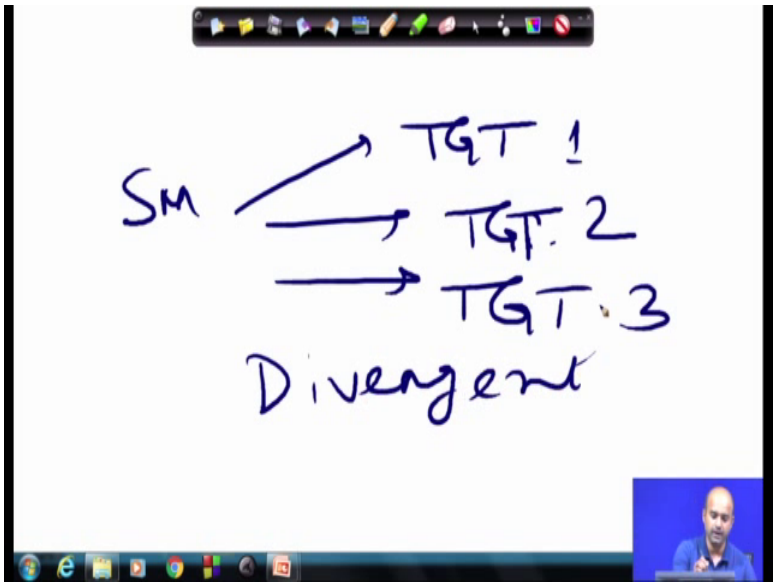

So, starting from a simple target molecule or simple starting material you can get target 1, target 2 or target 3. So, this will be target basically target 2 and target 3. So, these things you need to take care and this is basically a divergent pathway or triple divergent pathway this divergent sometimes give you a very nice demonstration.

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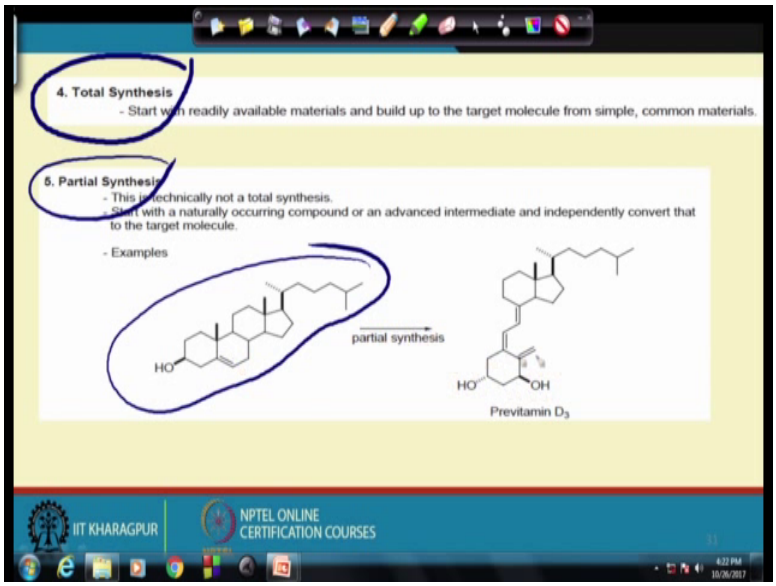

Other things we will try to cover in the section as I said this terminology is already known to you it is called total synthesis.

Somehow we have to make the molecule that is the final goal partial synthesis sometimes we use which means that you start with a known starting material which is available to you this material you are not making then use some normal transformations and get this final target molecule this is called partial synthesis.

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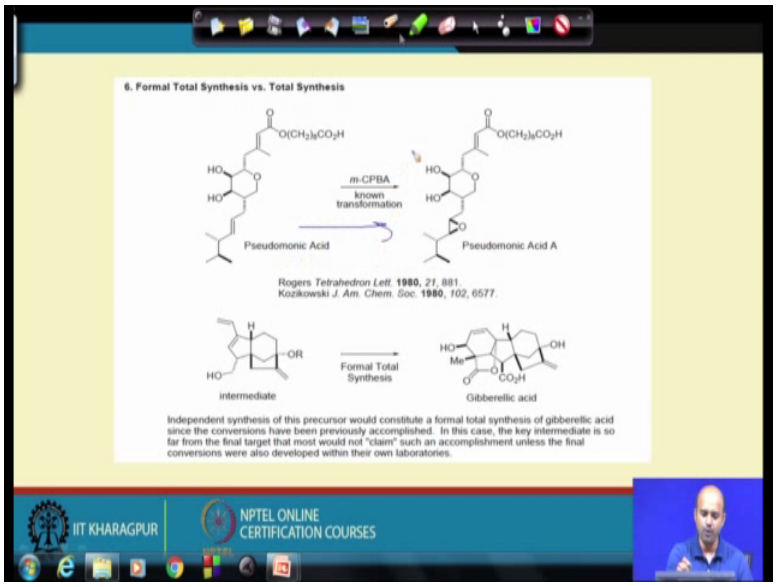

So, we will try to try to close down in this particular section and finally, we will talk about 2 terminologies which is name as formal total synthesis versus total synthesis formal means some steps are known. So, you are arrived up to this point you have arrived up to this point. So, you arrived up to particularly certain point by sub synthetic steps from this point the remaining steps are known.

These steps are basically known to you now this is called formal total synthesis sometimes this is very important and sometimes it happened that you are trying to do a biomimetic synthesis which is nothing, but how in the nature, natural products have been synthesized or mother nature how it made complex molecules that is called by biomimetic synthesis.

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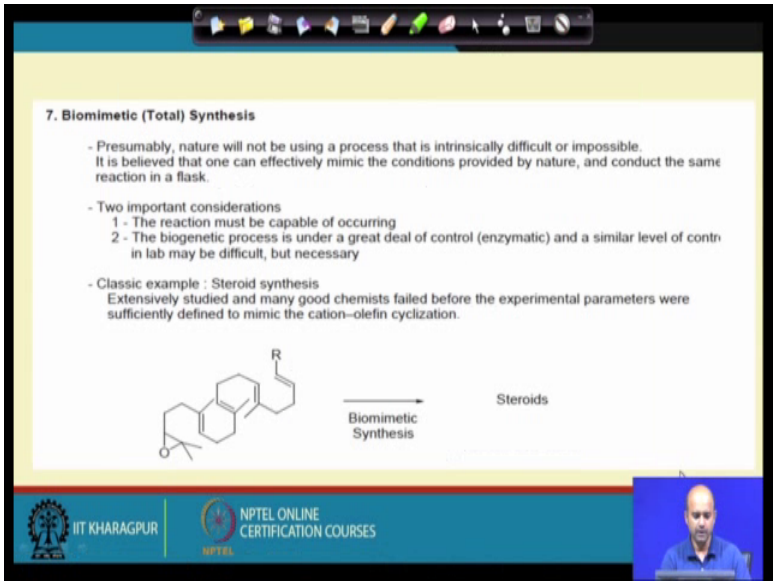

So, probably we will catch you in the next week and.

Thank thanks for being with us. So, stay tuned will be coming to you next week.